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(58) Field of search
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# (54) Metal complex salts and their use in diagnostic preparations

(57) A diagnostic preparation useful in a method of diagnosis using NMR, X-ray and ultra-sound, comprises (i) a physiologically tolerable complex salt which contains (a) a central element selected from elements having atomic numbers of from 21 to 29, 42, 44 and from 57 to 83, and (b) a radical of a physiologically-tolerable complex-forming acid and, if desired, (c) a radical selected from radicals of inorganic and organic bases and amino acids, and (ii) a physiologically tolerable carrier. The salts are claimed per se and may contain e.g. methylenephosphonic acid or aminoacetic acid type complexing acids. Metal complexes of monoclonal antibodies coupled with DTPA and CDTA are also prepared (Example 55).

GB 2 137 612 A

SPECIFICATION

**Diagnostic preparations and their use in a method of diagnosis**

The invention relates to diagnostic preparations and the use thereof in diagnosis.

Complex compounds and their salts have been used for a long time in medicine, for example as auxiliaries for the administration of sparingly soluble ions (for example iron) and as antidotes (calcium or zinc complexes being preferred in this case) for detoxication in the case of inadvertent incorporation of heavy metals or their radioactive isotopes.

We have now found that certain physiologically tolerable complex salts containing one or more central elements having the atomic numbers of from 21 to 29, 42, 44 and from 57 to 83 can be used for the manufacture of preparations that are surprisingly outstandingly suitable for use in NMR, ultra-sound and X-ray diagnostics.

The present invention provides a diagnostic preparation which comprises (i) a physiologically tolerable complex salt which contains (a) a central element selected from elements having atomic numbers of from 21 to 29 inclusive, 42, 44 and from 57 to 83 inclusive, and (b) a radical of a physiologically tolerable complex-forming acid and, if desired, (c) a radical selected from radicals of inorganic and organic bases and amino acids, and (ii) a physiologically tolerable carrier, especially an aqueous carrier.

The physiologically tolerable complex salt (i) may contain more than one central element and more than one of the radicals (b) and (c).

For the intended use of the diagnostic agent according to the invention, the element or elements having an atomic number mentioned above, which forms the central element or elements of the physiologically tolerably complex salt, must not, of course, be radioactive.

In the case where a preparation of the invention is to be used in NMR diagnostics (see European Patent Application 71 564), the central element of the complex salt must be paramagnetic. Such elements are especially the divalent and trivalent elements having an atomic number of from 21 to 29, 42, 44 and from 58 to 70. Suitable elements are, for example, chromium(III), manganese(II), iron(III), iron(II), cobalt(II), nickel(II), copper(II), praseodymium(III), neodymium(III), samarium(III) and ytterbium(III). Especially preferred, owing to their strong magnetic moment, are gadolinium(III), terbium(III), dysprosium(III), holmium(III) and erbium(III).

If the preparation of the invention is to be used in X-ray diagnostics, the central element must be one having a relatively high atomic number in order to obtain sufficient absorption of the X-rays. It has been found that diagnostic preparations that comprise a physiologically tolerable complex salt containing a central element or elements having an atomic number of from 57 to 83 are suitable for this purpose; such elements are, for example, lanthanum(III), the above-mentioned elements of the lanthanide series, gold(III), lead(II) or, especially, bismuth(III). Especially suitable are physiologically tolerable complex salts in which the central element (a) has an atomic number of from 71 to 83.

The preparation of the invention that are to be used in NMR diagnostics and those that are to be used in X-ray diagnostics are also suitable for use in ultrasound diagnostics.

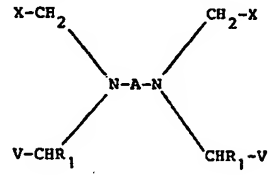
Suitable complex-forming acids are those which are customarily used for complex formation of the above-mentioned central elements. Suitable complex-forming acids are, for example, those which contain from 3 to 12, preferably from 3 to 8, methylenephosphonic acid groups, methylenecarbohydroxamic acid groups, carboxyethylidene groups or, especially, carboxymethylene groups of which at least one, two or three are bound to a nitrogen atom supporting the complex formation. If three of the acid groups are bonded to a nitrogen atom, then the complex-forming acids in question are those which form the basis of the complex salts of the general formula

$$N(CH_2X)_3 \qquad (II)$$

in which

X represents the radicals $-COOY$, $-PO_3HY$ or $-CONHOY$ wherein Y represents a hydrogen atom, a metal equivalent and/or a physiologically tolerable cation of an inorganic or organic base or amino acid, with the proviso that at least two of the substituents Y are metal equivalents in which the metal has an atomic number of from 21 to 29, 42, 44 or from 57 to 83.

If in each case only one or two of the acid groups are bonded to a nitrogen atom, then the nitrogen atom is bonded to a further nitrogen atom by way of optionally substituted ethylene or by way of up to four ethylene units each of which is separated by a nitrogen, oxygen or sulphur atom supporting the complex formation. Preferred complex-forming acids of that type are those forming the basis of complex salts of the general formula



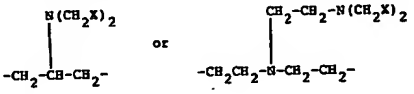

(I)

in which

X represents the radicals $-COOY$, $-PO_3HY$ or $-CONHOY$ wherein Y represents a hydrogen atom, a metal equivalent and/or a physiologically tolerable cation of an inorganic or organic base or amino acid,

and in which

A represents the group $-CHR_2-CHR_3-$, $-CH_2-CH_2-(ZCH_2-CH_2)_m-$,




in which

X has the meanings given above,

$R_1$ represents in each case a hydrogen atom or methyl group,

$R_2$ and $R_3$ together represent a trimethylene group or a tetramethylene group, or each represents a hydrogen atom, lower alkyl group, phenyl group or benzyl group, or

$R_2$ represents a hydrogen atom

and

$R_3$ represents a group $-(CH_2)_p-C_6H_4-W-$protein in which

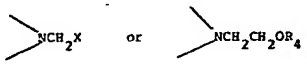
p represents 0 or 1,

W represents $-NN-$, $-NHCOCH_2-$ or $-NHCS-$ and

–protein represents a protein radical and

*m* represents the integer 1, 2 or 3,

Z represents an oxygen atom of a sulphur atom or the group



in which

X has the meanings given above and

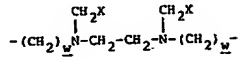
$R_4$ represent a lower alkyl group and in which

V has the same meaning as X or represents the group $-CH_2OH$, $-CONH(CH_2)_nX$ or $-COB$ in which

X has the meanings given above,

B represents a protein or lipid radical and

*n* represents the integers from 1 to 12 or if $R_1$, $R_2$ and $R_3$ are hydrogen atoms both V's together represent the group



in which

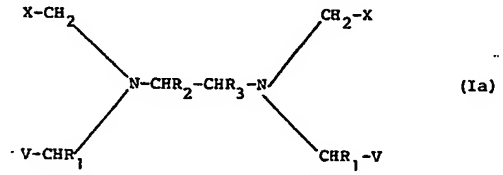
X has the meanings given above and

*w* represents the integer 1, 2 or 3,

with the proviso that at least two of the substituents Y are metal equivalents in which the metal has an atomic number of from 21 to 29, 42, 44 or from 57 to 83.

The complex-forming acids can, as conjugates, be bonded to biomolecules that are known to become especially concentrated in the organ or organ part under examination. Such biomolecules are, for example, hormones, such as insulin, prostaglandins, steroid hormones, amino sugars, peptides, proteins or lipids. There come into consideration more especially conjugates with albumens, such as humen serum albumen, antibodies, such as, for example, monoclonal antibodies specific to tumour-associated antigens, or antimyosin. The diagnostic preparations formed therefrom are suitable, for example, for use in tumour and infarct diagnosis. For examinations of the liver there are suitable, for example, conjugates or inclusion compounds with lipsomes, which are used, for example, as unilamellar or multilamellar phosphatidylcholine-cholesterol vesicles. The conjugates are formed either by way of a carboxy group of the complex-forming acid or, in the case of proteins or peptides, alsc by way of a $(CH_2)_p-C_6H_4-W-$ group as defind above under $R_3$. In the conjugate formation of some complex-forming acids with proteins, peptides or lipids, several acid radicals may be bonded to the macromolecular biomolecule. In that case, each complex-forming acid radical may carry one central elements. If the complex-forming acids are not bonded to biomolecules, they carry optionally two central elements, and especially one central element.

Suitable complex salts of the general formula I above are, for example, those of the general formula Ia

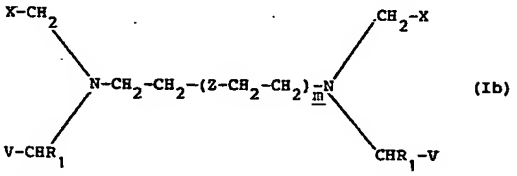


(Ia)

in which X, V, $R_1$, $R_2$ and $R_3$ have the meanings given above.

The following complex-forming acids, *inter alia*, are suitable for the manufacture of the complex salts of the general formula Ia:— ethylenediaminetetraacetic acid, ethylenediaminetetraacetohydroxamic acid, *trans*-1,2-cyclohexylenediaminetetraacetic acid, *DL*-2,3-butylenediaminetetraacetic acid, *DL*-1,2-butylenediaminetetraacetic acid, *DL*-1,2 propylenediaminetetraacetic acid, 1,2-diphenylethylenediaminetetraacetic acid, ethylenedinitrolotetrakis-(methanephosphonic acid) and N-(2-hydroxyethyl)-ethylenediaminetriacetic acid.

Other suitable complex salts of the general formula I are, for example, those of the general formula Ib

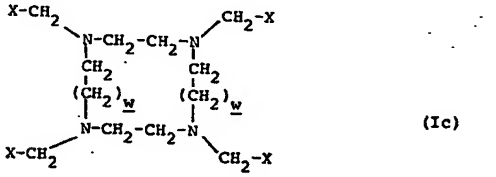


(Ib)

in which X, V, Z, $R_1$ and *m* have the meanings given above. If Z represents an oxygen atom or a sulphur atom, complex salts in which *m* represents 1 or 2 are preferred.

The following complex-forming acids, *inter alia*, are suitable for the manufacture of the complex salts of the general formula Ib: diethylenetriaminepentaacetic acid, triethylenetetraminehexaacetic acid, tetraethylenepentaamineheptaacetic acid, 13,23-dioxo-15,18,21-tris (carboxymethyl)-12,15,18,21,24-pentaazapentatriacontanoic diacid, 3,9-bis-(1-carboxyethyl)-3,6,9-triazaundecanoic diacid, diethylenetriaminepentakis (methylenephosphonic acid), 1,10-diaza-4,7-dioxadecane-1,1,10,10-tetraacetic acid and 1,10-diaza-4,7-dithiadecane-1,1,10,10-tetraacetic acid.

Suitable complex salts of the general formula I are also those of the general formula Ic



(Ic)

in which X and *w* have the meanings given above.

The following complex-forming acids, *inter alia*, are suitable for the manufacture of the complex salts of the general formula Ic:

1,4,8,11 - tetraazacyclotetradecanetetraacetic acid and, especially, 1,4,7,10 - tetraazacyclododecane-tetraacetic acid.

Other complex-forming acids that are suitable for the manufacture of the complex salts of the general formula I are, for example:

1,2,3 - tris - [bis - (carboxymethyl) - amino] - propane and nitrolotris - (ethylenenitrolo) - hexaacetic acid. As an example of a complex-forming acid for the manufacture of complex salts of the general formula II there may be mentioned nitrolotriacetic acid.

If not all of the acid hydrogen atoms of the complex-forming acid are substituted by the central element or elements, it is advantageous, for the purpose of increasing the solubility of the complex salt, to substitute the remaining hydrogen atoms by physiologically tolerable cations of inorganic and/or organic bases or amino acids. Suitable inorganic cations are for example, lithium, potassium or especially, sodium. Suitable cations of organic bases are, *inter alia*, those of primary, secondary or tertiary amines, such as, for example, ethanolamine, diethanolamine, morpholine, glucamine, N,N - dimethylglucamine or, especially, N - methylglucamine. Suitable cations of amino acids are, for example, those of lysine, arginine or onithine.

The complex-forming acids required for the diagnostic preparations of the invention are known or can be manufactured in a manner known *per se*.

For example, 13, 23 - dioxo - 15,18,21 - tris (carboxy-methyl) - 12,15,18,21 - 24 - pentaaza-pentatriacontanoic diacid is manufactured in the following manner, which is an improvement to the method proposed by R. A. Bulman *et al.* in Naturwissenschaften *68*, (1981) 483:

17.85 g (= 50 mmol) of 1,5 - bis - (2,6 - dioxomorpholino) - 3 - azapentane - 3 - acetic acid are suspended in 400 ml of dry dimethylformamide and, after the addition of 20.13 g (= 100 mmol) of 11 - aminoundecanoic acid, the whole is heated at 70°C for 6 hours. The clear solution is concentrated *in vacuo*. The yellow oily residue is stirred with 500 ml of water at room temperature. In so doing, an almost white, voluminous solid precipitates which is suction-filtered and washed several times with water. For further purification, the resulting product is introduced into 200 ml of acetone and the whole is stirred for 30 minutes at room temperature. After suction-filtering and drying *in vacuo* at 50°C, 36.9 g (= 97 % of the theoretical yield) of a white powder of melting point 134 - 138°C are obtained.

Conjugation of the complex-forming acids with biomolecules is likewise effected according to methods known *per se*, for example by reacting the nucleophilic groups of the biomolecule, such as, for example, amino, hydroxy, thio or imidazole groups, with an activated derivative of the complex-forming acid.

Activated derivatives of the complex-forming acid which come into consideration are, for example, acid chlorides, acid anhydrides, activated esters, nitrenes or isothiocyanates. Conversely, it is also possible to react an activated biomolecule with the complex-forming acid.

For conjugation with proteins, substituents of the structure $-C_6H_4N_2^+$ or $-C_6H_4NHCOCH_2$ halogen may also be considered.

The manufacture of some of the complex salts is likewise known or can be carried out in a manner known *per se* by dissolving or suspending the metal oxide or metal salt (for example the nitrate, chloride or sulphate) of the element having an atomic number of from 21 to 29, 42, 44 or from 57 to 83 in water and/or a lower alcohol (such as methanol, ethanol or isopropanol) and adding a solution or suspension of the equivalent amount of the complex-forming acid in water and/or a lower alcohol, and stirring, if necessary while warming or heating to boiling point, until the reaction is complete. If the complex salt formed is in soluble in the solvent used, it is isolated by filtration. If it is soluble, it can be isolated by concentrating the solution to dryness by evaporation, for example by means of spray-drying.

If acid groups are still present in the resulting complex salt, it is often advantageous to convert the acid complex salt into a neutral complex salt or salts by means of inorganic and/or organic bases or amino acids that form physiologically tolerable cations and to isolate the neutral salt. In many cases, this is indeed unavoidable since the dissociation of the complex salt is so suppressed by the shift in the pH value to neutral that only in that manner can uniform products be at all isolated or at least purified.

The manufacture is advantageously carried out with the aid of organic bases or basic amino acids. It can, however, also be advantageous if the neutralisation is carried out by means of inorganic bases (hydroxides, carbonates or bicarbonates) of sodium, potassium or lithium.

For the manufacture of the neutral salts there may, for example, be added to the acid complex salts in aqueous solution or suspension as much of the desired base as is necessary to obtain the neutral point. The resulting solution can subsequently be concentrated to dryness *in vacuo*. It is frequently of advantage to precipitate the resulting neutral salts by adding water-miscible solvents, such as, for example, lower alcohols (methanol, ethanol, isopropanol, etc.), lower ketones (acetone, etc.), and polar ethers (tetrahydrofuran, dioxane, 1,2 - dimethyoxyethane, etc.), and thus obtain crystallisates that are easily isolated and readily purified. It has been found especially advantageous to add the desired base to the reaction mixture during the complex formation and thereby dispense with one process step.

If the acid complex salts contain several free acid groups, it is often advantageous to produce neutral mixed salts that contain both inorganic and organic physiologically tolerable cations as ions of opposite charge. This can be effected, for example, by reacting the complex-forming acid in aqueous suspension or solution with the oxide or salt of the element supplying the central element and with half the amount of organic base required for neutralisation, isolating the complex salt formed, if desired purifying it, and then adding to it the amount of inorganic base

required for complete neutralisation. The order in which the bases are added can also be reversed.

The manufacture of the diagnostic preparations according to the invention is likewise effected in a manner known *per se* by suspending or dissolving the complex salts in an aqueous medium, optionally with the addition of the additives customary in galenical pharmacy, and subsequently sterilising the solution or suspension. Suitable additives are, for example, physiologically tolerable buffers (such as, for example, tromethamine hydrochloride), small additions of complex formers (such as, for example, diethylenetriaminepentaacetic acid) or, if necessary, electrolytes (such as, for example, sodium chloride).

In principle, it is also possible to manufacture the diagnostic preparations of the invention even without isolating the complex salts. In each case, particular care must be taken to effect the chelate formation in such a manner that the salts and salt solutions according to the invention are virtually free of non-complexed toxically acting metal ions. This can be ensured, for example, with the aid of colour indicators, such as xylenol orange, by test titrations during the manufacturing process. The invention also therefore provides processes for the manufacture of the complex salts and of the afore said preparations containing them. As a final safeguard, there is always purification of the isolated complex salt.

If suspensions of the complex salts in water or physiological salt solution are desired for oral administration or other purposes, a sparingly soluble complex salt is mixed with one or more auxiliaries customary in galenical pharmacy and/or surfactants and/or aromatic substances for taste correction.

The diagnostic preparations of the invention contain preferably from 1 µmol to 1 mol per litre of the complex salt and are, as a rule, administered in doses of from 0.001 to 5 mmol/kg. They are intended for oral, and especially parenteral, administration.

The diagnostic prepaarations of the invention meet the many requirements for suitability as contrast agents for nuclear spin tomography. For example, after oral or parenteral administration, they are outstandingly suitable for improving the information that can be provided by the image obtained with the aid of nuclear spin tomography, as a result of increasing the signal intensity. They also exhibit the high activity necessary to keep to a minimum the amount of foreign substances introduced into the body and the good tolerability necessary to maintain the noninvasive character of the examination (the compounds mentioned in J. Comput. Tomography *5*, 6: 543-46 (1981), in Radiology *144*, 343 (1982) and in Brevet Special de Medicament No. 484 M (1960) are, for example, too toxic). The ready water-solubility of the complex salts used in the preparations of the invention enables the preparation of highly concentrated solutions, so that the volume introduced into the circulation can be kept within reasonable limits and the dilution by body fluid can be compensated, that is to say the NMR diagnostic preparations must be 100 to 1000 times more water-soluble than is necessary for NMR spectroscopy. Furthermore, the diagnostic preparations of the invention are not only highly stable *in vitro* but also exhibit a surprisingly high stability *in vivo*, so that the *per se* toxic ions that are not covalently bonded in the complexes are released or exchanged only extremely slowly over the 24 hours in which, as pharmacological studies have shown, the novel contrast agents are completely eliminated. The conjugates with proteins and antibodies which are used, for example, for the diagnosis of tumours bring about a surprisingly high intensification of the signal at such a low dosage that it is possible to use in this case solutions of correspondingly low concentration.

The diagnostic preparations of the invention particularly those in which the physiologically complex salt contains an element having a relatively high atomic number that is from 57 to 83, for example 71 to 83, are also outstandingly suitable as X-ray contrast agents; it should be especially emphasised that, with these, none of the symptoms of anaphylaxy-type reactions known in the case of iodine-containing contrast agents can be detected in biochemical-pharmacological tests. They are especially valuable by virture of their advantageous absorption properties in regions of relatively high tube voltages for digital substraction techniques.

Further, the diagnostic preparations of the invention are also suitable as ultra-sound diagnostics owing to their property of favourably influencing the ultra-sound speed.

In contrast to conventional X-ray diagnostics with shadow-producing X-ray contrast agents, in NMR diagnostics with paramagnetic contrast agents there is *no* linear relationship between the signal intensification and the concentration used. As control studies have shown, increasing the dose administered does not necessarily result in the signal being intensified, and, in the case of a high dose of paramagnetic contrast agent, the signal can even be extinguised. It was, for that reason, surprising that some pathological processes become visible only after the administration of doses higher than those specified in EP 71 564 (which may be from 0.0001 mmol/kg to 5 mmol/kg) of a preparation of the invention containing a strongly paramagnetic contrast agent. Thus, for example, a defective blood-brain barrier in the region of a cranial abscess can be demonstrated only after giving 0.05 to 2.5 mmol/kg, preferably 0.1 — 0.5 mmol/kg, of paramagnetic complex salts such as, for example, gadolinium diethylenetriaminepentaacetic acid or manganese 1,2-cyclohexylenediaminetetraacetic acid in the form of its readily water-soluble salts. For a dose of more than 0.1 mmol/kg, solutions of higher concentrations of up to 1 mol/l, preferably from 0.25 to 0.75 mol/l, are required since only in this way is the volume reduced and the ease of handling the injection solution ensured.

Especially low doses (under 1 mg/kg) and therewith solutions of lower concentrations (1µmol/l to 5 mmol/l) than are specified in EP 71 564 are required for organ-specific NMR diagnostics, for example for detecting tumours and coronary infarts.

The invention also provides physiologicaly tolerable complex salts containing (a) a central element selected from elements having atomic numbers of from 21 to 29, 42, 44 and from 57 to 83, for example of

from 71 to 83, and (b) a radical of a physiologically tolerable complex-forming acid, and, if desired, (c) a radical selected from radicals of inorganic and organic bases and amino acids, for example a physiologically tolerable complex salt of the general formula I given above, in which X, A, V and $R_1$ have the meanings given above, with the proviso that it contains from 3 to 12 substituents Y of which at least two are metal equivalents in which the metal has an atomic number of from 21 to 29, 42, 44 or from 57 to 83 and, in addition, at least one of the substituents Y is a physiologically tolerable cation of an organic base or amino acid, any substituents Y which may remain being hydrogen atoms or cations of an inorganic base.

The present invention further provides a method of diagnosis using NMR, X-rays or ultra-sound, wherein a preparation of the present invention is administered to a human or animal body.

The following Examples illustrate the invention:—

*Example 1*

*Preparation of the gadolinium(III) complex of nitrolo-N,N,N-triacetic acid, $C_6H_6GdNO_6$*

A suspension of 36.2 g (= 100 mmol) of gadolinium oxide ($Gd_2O_3$) and 38.2 g (= 200 mmol) of nitrilotriacetic acid in 1.2 litres of water is heated, while stirring, to 90°C to 100°C and is stirred at this temperature for 48 hours. The undissolved material is filtered off over active carbon and the filtrate is concentrated to dryness by evaporation. The amorphous residue is pulverised.

Yield: 60 g (87 % of the theoretical yield) m.p. 300°C

gadolinium: calculated 45.5 %, found 44.9 %.

The iron(III) complex of nitrolo-N,N,N-triacetic acid is obtained in analogous manner with the aid of iron(III) chloride, $FeCl_3$.

In analogous manner there is obtained, using N-methylglucamine in place of sodium hydroxide solution,

the di-N-methylglucamine salt of the gadolinium(III) complex of 13,23-dioxo-15,18,21-tris(carboxymethyl)-12,15,18,21,24-pentaazapentatriacontanoic diacid, $C_{50}H_{96}GdN_7O_{22}$.

*Example 3*

*Preparation of the disodium salt of the gadolinium(III) complex of 3,9-bis(1-carboxyethyl)-6-carboxymethyl-3,6,9-triazaundecanoic diacid, $C_{16}H_{22}GdN_3O_{10}.2Na$*

36.2 g (= 0.1 mol) of gadolinium(III) oxide and 84.2 g (= 0.2 mol) of 3,9-bis(1-carboxyethyl)-6-carboxymethyl-3,6,9-triazaundecanoic diacid are suspended in 250 ml of water and the whole is refluxed for 1 hour. The small amount of undissolved material is filtered off and the solution is concentrated to dryness *in vacuo*. The residue is pulverised and dried *in vacuo* at 60°C. 112.8 g (= 98 % of the theoretical yield) of the complex salt (chelate) is obtained in the form of a white powder.

Analysis: $C_{16}H_{24}GdN_3O_{10}$

| | | | | |
|---|---|---|---|---|
| (calculated) | C 33.39 | H 4.20 | Gd 27.32 | N 7.30 |
| (found) | C 47.13 | H 6.83 | Gd 27.42 | N 7.21 |

*Example 2*

*Preparation of the disodium salt of the gadolinium(III) complex of 13,23-dioxo-15,18,21-tris-(carboxymethyl)-12,15,18,21,24-pentaazapentatriacontanoic diacid, $C_{36}H_{60}GdN_5O_{12}.2Na$.*

15.2 g (= 20 mmol) of 13,23-dioxo-15,18,21-tris-(carboxymethyl)-12,15,18,21,24-pentaazapentatriacontanoic diacid are suspended in 400 ml of water and the suspension is heated to 95°C. 7.43 g (= 20 mmol) of gadolinium(III) chloride hexahydrate, dissolved in 60 ml of water, are slowly added dropwise. The whole is maintained at this temperature for 2 hours and then, in order to neutralise the hydrochloric acid formed, 60 ml of 1N sodium hydroxide solution are added.

When the reaction is complete (testing with xylenol orange) the precipitate obtained is filtered and washed free of sodium chloride with water. 17.60 g (96 % of the theoretical yield) of a water-insoluble, white powder of melting point 290-292°C are obtained.

Gadolinium(III) complex of 13,23-dioxo-15,18,21-tris-(carboxymethyl)-12,15,18,21,24-pentaazapentatriacontanoic diacid.

Analysis:

| | | | | |
|---|---|---|---|---|
| (calculated) | C 47.30 | H 6.84 | N 7.66 | Gd 17.20 |
| (found) | C 47.13 | H 6.83 | N 7.60 | Gd 17.06 |

14.6g (= 16 mmol) of the gadolinium(III) complex so obtained are suspended in 200 ml of water, and 31.4 l of 1N sodium hydroxide solution are added dropwise thereto. After 1 hour a clear solution is obtained which is filtered and then concentrated *in vacuo*. After drying *in vacuo* at 80°C 13.2 g (87 % of the theoretical yield) of a readily water-soluble, white powder of melting point 279-285°C are obtained.

Analysis:

| | | | | | |
|---|---|---|---|---|---|
| (calculated) | C 45.13 | H 6.13 | N 7.31 | Gd 16.41 | Na 4.80 |
| (found) | C 45.20 | H 6.12 | N 7.28 | Gd 16.26 | Na 4.75 |

57.6 g (= 0.1 mol) of the complex salt are introduced into a solution of 0.1 mol of caustic soda in 100 ml of water. By adding a further 0.1 ml of caustic soda powder a pH of 7.5 is established in the solution, the solution is heated to boiling point and ethanol is added dropwise until the reaction mixture remains turbid. After stirring for several hours in an ice bath, the crystallisate is suction-filtered, washed with ethanol and dried *in vacuo*. The disodium salt is obtained in quantitative yield in the form of a white powder.

Analysis:

| | | | | |
|---|---|---|---|---|
| (calculated) | C 31.02 | H 3.58 | Gd 25.38 | N 6.78 |
| (found) | C 31.10 | H 3.71 | Gd 25.50 | N 6.61 |

*Example 4*

*Preparation of the dimorpholine salt of the gadolinium(III) complex of 3,9-bis-(1-carboxyethyl)-6-carboxymethyl-3,6,9-triazaundecanoic diacid, $C_{24}H_{42}GdN_5O_{12}$*

17.4 g (= 0.2 mol) of morpholine are dissolved in 50 ml of water. 42.1 g (= 0.1 mol) of 3,9-bis(1-carboxyethyl)-6-carboxymethyl-3,6,9-triazaundecanoic diacid and then 18.2 g (= 0.05 mol) of gadolinium(III) oxide are added and the whole is maintained at reflux temperature until a clear solution has appeared. Acetone is then added dropwise

until the reaction mixture remains turbid. After stirring for several hours in an ice bath, the crystallisate is suction-filtered, washed with acetone and dried *in vacuo*. The dimorpholine salt is obtained in quantitative yield in the form of a white powder.

Analysis:

| | | | | |
|---|---|---|---|---|
| (calculated) | C 38.44 | H 5.65 | Gd 20.97 | N 9.34 |
| (found) | C 38.31 | H 5.72 | Gd 20.76 | N 9.32 |

*Example 5*

*Preparation of the di - N - methylglucamine salt of the gadolinium(III) complex of diethylenetriamine - N,N,N',N",N" - pentaacetic acid, $C_{28}H_{54}GdN_5O_{20}$.*

39.3 g ( = 100 mmol) of diethylenetriamine - N,N,N',N",N" - pentaacetic acid are suspended in 200 ml of water, and 19.5 g ( = 100 mmol) of N - methylglucamine are added. 18.12 g ( = 50 mmol) of gadolinium(III) oxide, $Gd_2O_3$, are then added in portions and the resulting suspension is heated to 95°C. After approximately 1 hour, a further 19.5 g ( = 100 mmol) of N - methylglucamine are added and, after heating for a further 2 hours, a clear solution is obtained. When the reaction is complete (testing with xylenol orange), the small amount of undissolved material is filtered off and the filtrate is concentrated to dryness *in vacuo*. The residue is again dissolved in 100 ml of water and stirred into 250 ml of ethanol. After cooling for several hours, the crystallisate is suction-filtered, washed with cold ethanol and dried at 60°C *in vacuo*. 92.7 g (99 % of the theoretical yield) of a white powder of indeterminate melting point is obtained.

Analysis:

| | | | | |
|---|---|---|---|---|
| (calculated) | C 35.85 | H 5.80 | N 7.47 | Gd 16.77 |
| (found) | C 35.50 | H 5.72 | N 7.20 | Gd 67.54 |

For purification of the complex salt, it is possible to use, in place of ethanol, also acetone, propanol or isopropanol.

In analogous manner, there are obtained:
with dysprosium (III) oxide, $Dy_2O_3$, the di - N - methylglucamine salt of the dysprosium(III) complex of diethylenetriamine - N,N,N',N'',N'' pentaacetic acid, $C_{28}H_{54}DyN_5O_{20}$;
with lanthanum(III) oxide, $La_2O_3$,
the di - N - methylglucamine salt of the lanthanum(III) complex of diethylenetriamine - N,N,N',N",N" - pentaacetic acid, $C_{24}H_{54}LaN_5O_{20}$;
with ytterbium(III) oxide, $Yb_2O_3$,
the di - N - methylglucamine salt of the ytterbium(III) complex of diethylenetriamine - N,N,N',N",N" - pentaacetic acid, $C_{28}H_{54}YbN_5O_{20}$;
with samarium(III) oxide, $Sm_2O_3$,
the di - N - methylglucamine salt of the samarium(III) complex of diethylenetriamine - N,N,N',N",N" - pentaacetic acid, $C_{28}H_{54}SmN_5O_{20}$;
with holmium(III) oxide, $Ho_2O_3$,
the di - N - methylglucamine salt of the holmium(III) complex of diethylenetriamine - N,N,N',N",N" - pentaacetic acid, $C_{28}H_{54}HoN_5O_{20}$;
with bismuth(III) oxide, $Bi_2O_3$,
the di - N - methylglucamine salt of the bismuth(III) complex of diethylenetriamine - N,N,N',N",N" - pentaacitic acid, $C_{28}H_{54}BiN_5O_{20}$;
with gadolinium(III) oxide, $Gd_2O_3$,
the tri - N - methylglucamine salt of the gadolinium(III) complex of triethylenetetramine - N,N,N',N"N"',N"' - hexaacetic acid, $C_{39}H_{78}GdN_7O_{27}$.

There are also obtained in analogous manner:
with holmium(III) oxide, $Ho_2O_3$, and ethanolamine in place of N - methylglucamine,
the diethanolamine salt of the holmium(III) complex of diethylenetriamine - N,N,N',N",N" - pentaacetic acid, $C_{18}H_{34}HoN_5O_{12}$;
with gadolinium(III) oxide, $Gd_2O_3$, and lysine in place of N - methylglucamine,
the dilysine salt of the gadolinium(III) complex of diethylenetriamine - N,N,N',N",N" - pentaacetic acid, $C_{22}H_{42}HoN_5O_{14}$.

The salts are obtained in the form of a white powder of indeterminate melting point. They are very readily soluble in water.

*Example 6*

*Manufacture of the disodium salt of the gadolinium(III) complex of diethylenetriamine - N,N,N',N",N" - pentaacetic acid, $C_{14}H_{18}GdN_3O_{10}.2Na$*

*18.2 g ( = 0.05 mol) of gadolinium(III) oxide and 39.3 g ( = 0.1 mol) of diethylenetriaminepentaacetic acid are suspended in 110 ml of water and refluxed for 1 hour. The clear solution is cooled and adjusted to pH 7.5 by the addition of approximately 80 ml of 5N sodium hydroxide solution. The solution is again heated to boiling point and 250 ml of ethanol are added dropwise. After stirring for several hours in an ice bath, the crystallisate is suction-filtered, washed with ice-cold ethanol and dried at 60°C in vacuo.*

There is obtained in quantative yield a white powder which does not melt until 300°C.

Analysis:

| | | | | |
|---|---|---|---|---|
| (calculated) | C 28.43 | H 3.07 | N 7.10 | Gd 26.58 |
| (found) | C 28.35 | H 2.95 | N 7.05 | Gd 26.37 |

In analogous manner, there are obtained:
with dysprosium(III) oxide, $Dy_2O_3$,
the disodium salt of the dysprosium(III) complex of diethylenetriamine - N,N,N',N",N" - pentaacetic acid, $C_{14}H_{18}DyN_3O_{10}.2Na$;
with lanthanum(III) oxide, $La_2O_3$,
the disodium salt of the lanthanum(III) complex of diethylenetriamine - N,N,N',N",N" - pentaacetic acid, $C_{14}H_{18}LaN_3O_{10}.2Na$;
with holmium(III) oxide, $Ho_2O_3$,
the disodium salt of the holmium(III) complex of diethylenetriamine - N,N,N',N",N" - pentaacetic acid, $C_{14}H_{18}HoN_3O_{10}.2Na$;
with ytterbium(III) oxide, $Yb_2O_3$,
the disodium salt of the ytterbium(III) complex of diethylenetriamine - N,N,N',N',N" - pentaacetic acid, $C_{14}H_{18}YbN_3O_{10}.2Na$;
with samarium(III) oxide, $Sm_2O_3$,
the disodium salt of the samarium(III) complex of diethylenetriamine - N,N,N',N",N" - pentaacetic acid, $C_{14}H_{18}SmN_3O_{10}.2Na$;
with erbium(III) oxide, $Eb_2O_3$,
the disodium salt of the erbium(III) complex of diethylenetriamine - N,N,N',N",N" - pentaacetic acid, $C_{14}H_{18}EbN_3O_{10}.2Na$;
with gladolinium(III) oxide, $Gd_2O_3$,
the sodium salt of the digadolinium(III) complex of tetraethylenepentamine - N,N,N',N",N"',N'$^{V}$,N'$^{V}$ - heptaacetic acid, $C_{22}H_{30}Gd_2N_5O_{14}.Na$.

These salts are obtained as a white powder of indeterminate melting point and are very readily

soluble in water.

*Example 7*

*Manufacture of the N-methylglucamine salt of the iron(III) complex of diethylenetriaminepentaacetic acid, $C_{21}H_{37}FeN_4O_{15}$*

35.4 g (= 90 mmol) of diethylenetriaminepentaacetic acid are suspended in 100 ml of water, and 24.3 g (= 90 mmol) of iron(III) chloride hexahydrate ($FeCl_3 . 6 H_2O$), dissolved in 100 ml of water, are added thereto. The initially dark brown suspension is heated to 95°C. After approximately 1 hour, the colour changes to a light yellow. 270 ml of 1N sodium hydroxide solution are added to neutralise the hydrochloric acid formed and the whole is heated for a further 3 hours at 95°C. The resulting light yellow precipitate is suction-filtered, washed free of chloride with water and dried at 60°C *in vacuo*. 17.85 g (45 % of the theoretical yield) of a light yellow powder is obtained the melting point of which is > 300°C.

17.85 g (= 40 mmol) of the iron(III) complex salt obtained are suspended in 200 ml of water, and 7.8 g (= 40 mmol) of solid N-methylglucamine are added in portions. The whole is heated for approximately 3 hours at 50°C and an almost clear, red-brown solution is obtained which is filtered and then concentrated to dryness *in vacuo*. The residue is dried at 50°C *in vacuo*. 24.3 g (95 % of the theoretical yield) of a red-brown powder of melting point 131-133°C are obtained.

Analysis:

| | | | | |
|---|---|---|---|---|
| (calculated) | C 39.82 | H 5.89 | N 8.85 | Fe 8.81 |
| (found) | C 39.70 | H 6.00 | N 8.65 | Fe 9.01 |

By using sodium hydroxide solution in place of the N-methylglucamine there are obtained in analogous manner;

the sodium salt of the iron(III) complex of ethylenediaminetetraacetic acid, $C_{10}H_{12}FeN_2O_8 . Na$;

the sodium salt of the iron(III) complex of *trans*-1,2-cyclohexylenediaminetetraacetic acid, $C_{14}H_{18}FeN_2O_8 . Na$;

the disodium salt of the iron(III) complex of diethylenetrinitrolopenta (methanephosphonic acid), $C_9H_{23}FeN_3O_{15}P_5 . 2 Na$;

the sodium salt of the iron(III) complex of 1,10-diaza-4,7-dioxadecane-1,1,10,10-tetraacetic acid, $C_{14}H_{20}FeN_2O_{10} . Na$;

the sodium salt of the iron(III) complex of ethylenediaminetetraacetohydroxamic acid, $C_{10}H_{16}FeN_6O_8 . Na$.

In analogous manner, there are obtained with N-methylglucamine:

the di-N-methylglucamine salt of the iron(III) complex of diethylenetriamine-N,N,N',N'',N''-pentaacetic acid, $C_{28}H_{54}FeN_5O_{20}$;

the N-methylglucamine salt of the iron(III) complex of *trans*-1,2-cyclohexylenediamine-N,N,N',N'-tetraacetic acid, $C_{21}H_{36}FeN_3O_{13}$;

the N-methylglucamine salt of the iron(III) complex of ethylenediamine-N,N,N',N'-tetraacetic acid, $C_{17}H_{30}Fe_3O_{13}$;

the tri-N-methylglucamine salt of the iron(III) complex of triethylentetramine-N,N,N',N'',N''',N'''-hexaacetic acid, $C_{39}H_{78}FeN_7O_{27}$.

By using diethanolamine in place of N-methylglucamine there is obtained in analogous manner:

the di-diethanolamine salt of the iron(III) complex of diethylenetriamine-N,N,N'',N'',N''-pentaacetic acid, $C_{22}H_{42}FeN_5O_{14}$.

*Example 8*

*Manufacture of the N-methylglucamine salt of the gadolinium(III) complex of trans-1,2-cyclohexylenediamine-N,N,N',N'-tetraacetic acid, $C_{21}H_{36}GdN_3O_{13}$*

20.78 g (= 60 mmol) of *trans*-1,2-cyclohexylenediamine-N,N,N',N'-tetraacetic acid are suspended in 150 ml of water. After the addition of 11.7 g (= 60 mmol) of N-methylglucamine, an almost clear solution is obtained to which 10.88 g (= 30 mmol) of gadolinium oxide ($Gd_2O_3$) are added. The suspension again obtained is heated for 6 hours at 95°C. The small amount of undissolved material is filtered off and the filtrate is concentrated to dryness *in vacuo*.

The residue is dried *in vacuo* at 60°C and pulverised. 38.6 g (92 % of the theoretical yield) of a white powder of melting point 258-261°C are obtained.

Analysis:

| | | | | |
|---|---|---|---|---|
| (calculated) | C 36.25 | H 5.22 | N 6.04 | Gd 22.60 |
| (found) | C 36.40 | H 5.50 | N 5.98 | Gd 22.52 |

In analogous manner, by using sodium hydroxide solution in place of N-methylglucamine, the sodium salt of the gadolinium(III) complex of *trans*-1,2-cyclohexylenediamine-N,N,N',N'-tetraacetic acid, $C_{14}H_{18}GdN_2O_8 . Na$, is obtained.

By using freshly precipitated chromium(III) hydroxide, $Cr(OH)_3$, the sodium salt of the chromium(III) complex of ethylenediamine-N,N,N',N'-tetraacetic acid, $C_{10}H_{12}CrN_2O_8 . Na$, is obtained.

*Example 9*

*Preparation of the disodium salt of the manganese(II) complex of trans-1,2-cyclohexylenediamine-N,N,N',N'-tetraacetic acid, $C_{14}H_{16}MnN_2O_8 . 2 Na$*

Under nitrogen, 34.6 g 8 = 100 mmol) of *trans*-1,2-cyclohexylenediamine-N,N,N',N'-tetraacetic acid are suspended in 100 ml of water, and 11.5 g (= 100 mmol) of manganese(II) carbonate, $MnCO_3$, are added. The whole is heated to 95°C and 200 ml of 1N sodium hydroxide solution are added dropwise thereto. The clear solution is concentrated *in vacuo* and the residue is dried *in vacuo* at 60°C. 40.8 g (92 % of the theoretical yield) of a pink-coloured powder are obtained.

Analysis:

| | | | | |
|---|---|---|---|---|
| (calculated) | C 37.94 | H 4.09 | N 6.32 | Mn 12.40 |
| (found) | C 37.78 | H 4.12 | N 6.20 | Mn 12.31 |

In analogous manner, there are obtained:

from copper(II) carbonate the disodium salt of the copper(II) complex of *trans*-1,2-cyclohexylenediaminetetraacetic acid, $C_{14}H_{18}CuN_2O_8 . 2 Na$;

from cobalt(II) carbonate the disodium salt of the cobalt(II) complex of *trans*-1,2-cyclohexylenediaminetetraacetic acid, $C_{14}H_{18}CoN_2O_8 . 2 Na$;

from nickel(II) carbonate the disodium salt of the nickel(II) complex of *trans*-1,2-cyclohexylenediaminetetraacetic acid, $C_{14}H_{18}NiN_2O_8 . 2 Na$.

By using N-methylglucamine in place of sodium hydroxide solution there are obtained:

the di-N-methylglucamine salt of the manganese(II) complex of *trans*-1,2-cyclohexylenediaminetetraacetic acid, $C_{28}H_{54}MnN_4O_{18}$;

the di - N - methylglucamine salt of the manganese(II) complex of *DL* - 2,3 - butylenediaminetetraacetic acid, $C_{26}H_{52}MnN_4O_{18}$;
the di - N - methylglucamine salt of the manganese(II) complex of ethylenediamine - N,N,N',N' - tetraacetic acid, $C_{24}H_{48}MnN_4O_{18}$;
the di - N - methylglucamine salt of the manganese(II) complex of *DL* - 1,2 - butylenediamine - N,N,N',N' - tetraacetic acid, $C_{26}H_{52}MnM_4O_{18}$;
the di - N - methylglucamine salt of the manganese(II) complex of *DL* - 1,2 - propylenediamine - N,N,N',N' - tetraacetic acid, $C_{25}H_{50}MnN_4O_{18}$;
the tri - N - methylglucamine salt of the manganese(II) complex of diethylenetriaminepentaacetic acid, $C_{35}H_{72}MnN_6O_{25}$;

with nickel(II) carbonate, $NiCo_3$, there is obtained:
the di - N - methylglucamine salt of the nickel(II) complex of ethylenediamine - N,N,N',N' - tetraacetic acid, $C_{24}H_{48}NiN_4O_{18}$;

with cobalt(II) carbonate, $CoCO_3$, there is obtained:
the diethanolamine salt of the cobalt(II) complex of ethylenediamine - N,N,N',N' - tetraacetic acid, $C_{14}H_{28}CoN_4O_{10}$;

with copper(II) carbonate, $CuCO_3$, and ethanolamine there is obtained:
the diethanolamine salt of the copper(II) complex of ethylenediamine - N,N,N',N' - tetraacetic acid, $C_{14}H_{28}CuN_4O_{10}$;

with manganese(II) carbonate, $MnCO_3$, and diethanolamine there is obtained:
the tri-diethanolamine salt of the manganese(II) complex of diethylenetriamine - N,N,N',N'',N'' - pentaacetic acid, $C_{26}H_{54}MnN_6O_{16}$;

with manganese(II) carbonate, $MnCO_3$, and morpholine there is obtained:
the dimorpholine salt of the manganese(II) complex of ethylenediamine - N,N,N'',N'' - tetraacetic acid, $C_{18}H_{32}MnN_4O_{10}$.

*Example 10*

*Preparation of the N - methylglucamine salt of the gadolinium(III) complex of ethylenediamine - N,N,N',N' - tetraacetic acid, $C_{17}H_{30}GdN_3O_{13}$*

29.2 g (= 100 mmol) of ethylenediamine - N,N,N',N' - tetraacetic acid are suspended in 100 ml of water and heated to 95°C with 18.1 g (= 50 mmol) of gadolinium(III) oxide, $Gd_2O_3$. During the heating-up process, 19.5 g (= 100 mmol) of N -methylglucamine are added in portions. After approximately 3 hours, a clear solution is obtained which is filtered and concentrated to dryness *in vacuo*. The residue is dried at 60°C *in vacuo*. 61.3 g (95 % of the theoretical yield) of a white powder having an indeterminate melting point are obtained.

Analysis:

| | | | | |
|---|---|---|---|---|
| (calculated) | C 31.82 | H 4.71 | N 6.55 | Gd 24.51 |
| (found) | C 31.65 | H 4.59 | N 6.52 | Gd 24.56 |

In analogous manner, there are obtained:
with dysprosium(III) oxide $Dy_2O_3$:
the N - methylglucamine salt of the dysprosium(III) complex of ethylenediamine - N,N,N',N' - tetraacetic acid, $C_{17}H_{30}DyN_3O_{13}$.

By using 1,10 - diaza - 4,7 - dioxadecane - 1,1,10,10 - tetraacetic acid in place of ethylenediamine - N,N,N',N' - tetraacetic acid there is obtained:
the N - methylglucamine salt of the gadolinium(III) complex of 1,10 - diaza - 4,7 - dioxadecane - 1,1,10,10 - tetraacetic acid, $C_{21}H_{38}GdN_3O_{15}$;

Similarly, by using 1,2 - diphenylethylenediaminetetraacetic acid there is obtained:
the N - methylglucamine salt of the gadolinium(III) complex of 1,2 - diphenylethylenediaminetetraacetic acid, $C_{29}H_{38}N_3O_{13}Gd$;

By using lead(II) oxide, PbO, and sodium chloride, there is obtained:
the disodium salt of the lead(II) complex of ethylenediaminetetraacetic acid, $C_{10}H_{12}N_2O_8Pb$ . 2 Na;

By using freshly precipitated chromium(III) hydroxide, $Cr(OH)_3$, there is obtained:
the sodium salt of the chromium(III) complex of ethylenediaminetetraacetic acid, $C_{10}H_{12}CrN_2O_8$ . Na;
and analogously:
the sodium salt of the gadolinium (III) complex of ethylenediaminetetraacetohydroxamic acid, $C_{10}H_{16}GdN_6O_8$ . Na; and
the sodium salt of the gadolinium(III) complex of ethylenediamine - N,N,N',N' - tetraacetic acid, $C_{10}H_{12}GdN_2O_8$ . Na.

*Example 11*

*Preparation of the sodium salt of the gadolinium(III) complex of 1,4,7,10 - tetraazacyclododecane - N,N',N'',N''' - tetraacetic acid, $C_{16}H_{24}GdN_4O_8$ . Na*

4.0 g (= 10 mmol) of 1,4,7,10 - tetraazacyclododecane - N,N',N'',N''' - tetraacetic acid are suspended in 20 ml of water, and 10 ml of 1N sodium hydroxide solution are added. 1.8 g (= 5 mmol) of gadolinium(III) oxide, $Gd_2O_3$, are added and the suspension is heated for 2 hours at 50°C. The clear solution is filtered and concentrated *in vacuo*. The residue is dried and pulverised. 5.5 g (95 % of the theoretical yield) of a white powder are obtained.

Analysis:

| | | | | |
|---|---|---|---|---|
| (calculated) | C 33.10 | H 4.17 | N 9.65 | Gd 27.08 |
| (found) | C 33.01 | H 4.20 | N 9.57 | Gd 27.16 |

In analogous manner there are obtained:
the N - methylglucamine salt of the gadolinium(III) complex of 1,4,7,10 - tetraazacyclododecane - N,N',N'',N''' - tetraacetic acid, $C_{23}H_{42}GdN_5O_{13}$;
the sodium salt of the gadolinium(III) complex of 1,4,8,11 - tetraazacyclotetradecane - N,N',N'',N''' - tetraacetic acid, $C_{18}H_{28}GdN_4O_8$ . Na.

*Example 12*

*Preparation of the tetra - N - methylglucamine salt of the gadolinium(III) complex of ethylenedinitrolotetrakis (methanephosphonic acid),*

*$C_{34}H_{85}GdN_6O_{32}P_4$*

9.11 g (= 20 mmol) of ethylenedinitrolotetrakis (methanephosphonic acid) are suspended in 150 ml of water and the suspension is adjusted to a pH of 5 with the corresponding amount of N - methylglucamine. 3.6 g (= 10 mmol) of gadolinium(III) oxide, $Gd_2O_3$, are added thereto and the whole is heated to 70°C. After approximately 1 hour, a clear solution is obtained to which there is added the remaining portion of the N - methylglucamine. A total of 15.6 g (= 80 mmol) of N - methylglucamine is used. The solution is concentrated to dryness *in vacuo* and the gel-like residue remaining is introduced into 200 ml of acetonitrile. The mixture is stirred for approximately 20 hours at 30°C and the resulting fine precipitate is suction-filtered. After drying *in vacuo* at 40°C, 23.4 g

(85 % of the theoretical yield) of a white powder of melting point 115-118°C are obtained.
Analysis:

| | | | | | |
|---|---|---|---|---|---|
| (calculated) | C 29.78 | H 6.25 | N 6.13 | P 9.04 | Gd 11.47 |
| (found) | C 29.85 | H 6.57 | N 5.98 | P 8.78 | Gd 11.26 |

In analogous manner there are obtained:
the hepta - N - methylglucamine salt of the gadolinium(III) complex of dietheylenetriamine - N,N,N',N",N" - penta (methanephosphonic acid), $C_{58}H_{144}GdN_{10}O_{50}P_5$,
and, by using sodium hydroxide solution in place of N - methylglucamine.
the disodium salt of the gadolinium(III) complex of diethylene - trinitrolo - penta (methanephosphonic acid), $C_9H_{23}GdN_3O_{15}P_5 . 2\,Na$.

*Example 13*

*Preparation of the disodium salt of the manganese(II) complex of ethlyenedinitrolo - tetra (acetohydroxamic acid), $C_{10}H_{16}MnN_6O_8 . 2\,Na$*

2.30 g of manganese(II) carbonate and 7.05 g of ethylenedinitrolo - tetra (acetohydroxamic acid) are refluxed in 18 ml of water for 3 hours. The pH is then adjusted to 7 by the addition of dilute sodium hydroxide solution and 40 ml of acetone are added dropwise. After stirring for several hours in an ice bath, the crystallisate which has separated is suction-filtered, washed with acetone and dried at 50°C *in vacuo*. A dihydrate is obtained in quantitative yield in the form of a white powder having a melting point above 300°C.

| | | |
|---|---|---|
| Mn: | (calculated) | 11.30 |
| | (found) | 11.12 |

*Example 14*

*Preparation of a mixed salt solution comprising the sodium and the N - methylglucamine salt of the gadolinium(III) complex of diethylenetriamine-pentaacetic acid*

*a) preparation of the mono - N - methylglucamine salt of the complex, $C_{21}H_{37}GdN_4O_{15}$*

195.2 g (1 mol) of N - methylglucamine are dissolved in 7 litres of water. 393.3 g (1 mol) of diethylenetriaminepentaacetic acid and 181.3 g (0.5 mol) of gadolinium(III) oxide, $Gd_2O_3$, are added and whole is refluxed for 2 hours. The filtered clear solution is spray-dried. A white crystalline powder having a water content of 2.6 %, which sinters at 133°C and melts, with foaming, at 190°C is obtained.

| | | |
|---|---|---|
| Gd: | (calculated) | 21.17 |
| | (found) | 21.34 |

*b) preparation of the neutral mixed salt solution*

730.8 g (= 1 mol) of the salt obtained in a) are suspended in 630 ml of water *p.i. (pro injections)*, and 40 g (= 1 mol) of caustic soda powder are added in portions. The neutral solution is made up to 1000 ml with water *p.i.*, introduced into bottles over a pyrogen filter and heat-sterilised. This 1 molar solution contains 753.8 g of the mixed salt per litre.

*Example 15*

*Preparation of a solution of the di - N - methylglucamine salt of the gadolinium(III) complex of diethylenetriaminepentaacetic acid*

535.0 g (= 730 mmol) of the salt described in Example 5 are made into a paste in 500 ml of water *p.i.* and dissolved by adding 142.4 g (= 730 mmol) of N - methylglucamine at pH 7.2. The solution is then made up to 1000 ml with water *p.i.*, is introduced into ampoules and heat-sterilised.

*Example 16*

*Preparation of a solution of the disodium salt of the gadolinium(III) complex of diethylenetriamine-pentaacetic acid*

485.1 g (= 820 mmol) of the disodium salt obtained in Example 6 are made into a paste in 500 ml of water *p.i.*. The volume is then made up to 1000 ml with water *p.i.* and the solution is introduced into ampoules and heat-sterilised.

*Example 17*

*Preparation of a solution of the disodium salt of the gadolinium(III) complex of 13,23 - dioxo - 15,18,2 - tris - (carboxymethyl) - 12,15,18,21,24 - pentaaza-pentatriacontanoic diacid*

392.0 g (= 400 mmol) of the salt described in Example 2 are made into a paste in 500 ml of water *p.i.* and dissolved by making up the volume to 1000 ml with water *p.i.* while heating slightly. The solution is placed in bottles and heat-sterilised.

*Example 18*

*Preparation of a solution of the N - methylglucamine salt of the gadolinium(III) complex of 1,4,7,10 - tetraazacyclodecanetetraacetic acid*

370.9 g (= 500 mmol) of the complex salt described in Example 11 are made into a paste in 500 ml of water *p.i.* and dissolved by making up the volume to 1000 ml with water *p.i.*. The solution is introduced into ampoules and heat-sterilised.

*Example 19*

*Preparation of a solution of the di - N - methylglucamine salt of the manganese(II) complex of trans - 1,2 - cyclohexylenediaminetetraacetic acid*

395.9 g (= 500 mmol) of the complex salt described in Example 9 are suspended in 500 ml of water *p.i.*. 1.3 g of ascorbic acid are added and the suspension is dissolved by making up the volume to 1000 ml with water *p.i.*. The solution is sterile-filtered and placed in ampoules.

*Example 20*

*Preparation of a solution of the tri - N - methylglucamine salt of the manganese(II) complex of diethylene-triaminepentaacetic acid*

514.4 g (= 500 mmol) of the complex salt described in Example 9 are suspended in 600 ml of water *p.i.*. 1.3 g of ascorbic acid are added and the solid matter is dissolved by making up the volume to 1000 ml with water *p.i.*. After being sterile-filtered, the solution is placed in ampoules.

*Example 21*

*Preparation of a solution of the di - N - methyl-glucamine salt of the iron (III) complex of diethylenetriaminepentaacetic acid*

44.6 g (= 0.1 mol) of the iron(III) complex of diethylenetriaminepentaacetic acid obtained in Example 7 are suspended in 40 ml of water *p.i.*. After the

addition of 0.18 g of tromethamine hydrochloride and 39.1 g (= 0.2 mol) of N-methylglucamine, the solid matter is dissolved at the neutral point, the solution is made up to 100 ml with water *p.i.*, introduced into ampoules and heat-sterilised.

*Example 22*

*Preparation of a solution of the gadolinium(III) complex of nitrolotriacetic acid*

1.9 g (= 10 mmol) of nitrolotriacetic acid and 1.8 g (= 5 mmol) of gadolinium(III) oxide are dissolved in 100 ml of water *p.i.* while heating. The solution is introduced into ampoules and heat-sterilised.

*Example 23*

*Preparation of a solution of the N-methylglucamine salt of the gadolinium(III) complex of ethylenediaminetetraacetic acid*

38.52 g (= 60 mmol) of the substance described in Example 10 are dissolved in 70 ml of water *p.i.*. After the addition of 0.12 g of tromethamine, the solution is made up to 100 ml with water *p.i.*, placed in ampoules and heat-sterilised.

*Example 24*

*Preparation of a solution of the di-N-methylglucamine salt of the dysprosium(III) complex of diethylenetriaminepentaacetic acid*

35.7 g (= 60 mmol) of the dysprosium(III) complex of diethylenetriaminepentaacetic acid (water content 8.0 %) are suspended in 70 ml of water *p.i.* and dissolved at pH 7.5 by adding 21.2 g (= 120 mmol) of N-methylglucamine. The solution is then made up to 100 ml with water *p.i.*, placed in ampoules and heat-sterilised.

*Example 25*

*Preparation of a solution of N-methylglucamine salt of the gadolinium(III) complex of trans-1,2-cyclohexylenediaminetetraacetic acid*

555.8 g (= 0.8 mol) of the salt described in Example 8 are dissolved in water *p.i.* to a volume of 1000 ml. After filtration over a pyrogen filter, the solution is placed in ampoules and heat-sterilised.

*Example 26*

*Preparation of a solution of the N-methylglucamine salt of the ruthenium(III) complex of 1,10-diaza-4,7-dithiadecane-1,1,10,10-tetraacetic acid*

15.6 g (= 0.03 mmol) of the ruthenium(III) complex of 1,10-diaza-4,7-dithiadecane-1,1,10,10-tetraacetic acid are suspended in 50 ml of water *p.i.* and dissolved at pH 7.5 by adding 5.9 g (= 0.03 mol) of N-methylglucamine. The solution is made up to 1000 ml with water *p.i.*, placed in ampoules and heat-sterilized.

*Example 27*

*Preparation of a solution of the dilysine salt of the gadolinium(III) complex of diethylenetriaminepentaacetic acid*

273.8 g (= 0.5 mol) of the gadolinium(III) complex of diethylenetriaminepentaacetic acid are suspended in 500 ml of water *p.i.*. 292.4 g (= 1 mol) of lysine are added, the whole is stirred for several hours while heating gently and the volume is then made up to 1000 ml with water *p.i.*. The solution is placed in bottles and heat-sterilised.

*Example 28*

*Preparation of a solution of the tri-N-methylglucamine salt of the molybdenum(VI) complex of diethylenetriaminepentaacetic acid*

18.8 g (= 0.28 mol) of the complex $H_3[Mo_2O_2(OH)_4 \cdot C_{14}H_{23}N_3O_{10}]$ are suspended in 50 ml of water *p.i.* and dissolved at the neutral point by adding 16.4 g (= 0.84 mol) of N-methylglucamine. 0.15 g of tromethamine is added, the solution is made up to 100 ml with water *p.i.*, subjected to sterile filtration and placed in ampoules.

*Example 29*

*Preparation of a solution of the disodium salt of the manganese(II) complex of ethylenediaminetetraacetic acid*

343,2 g (= 1 mol) of the manganese(II) complex of ethylenediaminetetraacetic acid are suspended in 500 ml of water *p.i.* and dissolved at the neutral point by adding, in portions, 80 g (= 2 mol) of caustic soda. After the addition of 1.5 g of tromethamine, the solution is made up to 1000 ml with water *p.i.*, placed in bottles and heat-sterilised.

*Example 30*

*Preparation of a solution of the sodium salt of the iron(III) complex of ethylenediaminetetraacetic acid*

345.7 g (= 1 mol) of the iron(III) complex of ethylenediaminetetraacetic acid are suspended in 500 ml of water *p.i.* and dissolved at the neutral point by adding, in portions, 40 g (= 1 mol) of caustic soda. After the addition of 1.5 g of tromethamine, the solution is made up to 1000 ml with water *p.i.*, placed in bottles and heat-sterilised.

*Example 31*

*Preparation of a solution of the disodium salt of the iron(III) complex of dietheylenetriaminepentaacetic acid*

334.6 G (= 0.75 mol) of the iron(III) complex of diethylenetriaminepentaacetic acid are suspended in 500 ml of water p.i. and dissolved at the neutral point by adding, in portions, 60 g (= 1.5 mol) of caustic soda. The solution is made up to 1000 ml with water *p.i.*, placed in bottle and heat-sterilised.

*Example 32*

*Preparation of a solution of the sodium salt of the gadolinium(III) of trans-1,2 cyclohexylenediaminetetraacetic acid*

558.6 g (= 1 mol) of the sodium salt of the complex salt listed in Example 8 are dissolved in water *p.i.* and made up to 1000 ml. The solution is placed in bottles and heat-sterilised.

*Example 33*

*Preparation of a solution of the N-methylglucamine salt of the gadolinium(III) complex of 1,2-diphenylethylenediaminetetraacetic acid*

396.9 g (= 500 mmol) of the N-methylglucamine salt of the complex salt containing gadolinium and the 1,2-diphenylethylenediaminetetraacetic acid radical listed in Example 10 are made into a paste in 600 ml of water *p.i.* and dissolved by making up the volume to 1000 ml. The solution is placed in ampoules and heat-sterilised.

*Example 34*

*Preparation of a solution of the sodium salt of the iron (III) complex of ethylenediaminetetraacetic acid*

183.5 g (= 500 mmol) of the sodium salt of the complex salt of iron and ethylenediaminetetraacetic acid listed in Example 7 are made into a paste in 500 ml of water *p.i.*. 1.0 g of tromethamine are added, the

volume is made up to 1000 ml with water *p.i.*, and the solution is placed in ampoules and heat-sterilised.

*Example 35*

*Preparation of a solution of the di - N - methylglucamine salt of the lanthanum(III) complex of diethylenetriaminepentaacetic acid*

459.8 g (= 500 mmol) of the di - N - methylglucamine salt of the complex salt containing lanthanum and the diethylenetriaminepentaacetic acid radical listed in Example 5 are made into a paste in 650 ml of water *p.i.* and dissolved by making up the volume to 1000 ml with water *p.i.*. The solution is placed in ampoules and heat-sterilised.

*Example 36*

*Preparation of a solution of the di - N - methylglucamine salt of the bismuth(III) complex of diethylenetriaminepentaacetic acid*

692.8 g (= 700 ml) of the di - N- methylglicamine salt of the complex salt containing bismuth and the diethylenetriaminepentaacetic acid radical listed in Example 5 are made into a paste in 600 ml of water *p.i.* and, after the addition of 1.8 g of tromethamine, dissolved by making up the volume to 1000 ml with water *p.i.* while heating slightly. The solution is placed in ampoules and heat-sterilised.

*Example 37*

*Preparation of a solution of the di - N - methylglucamine salt of the holmium(III) complex of diethylenetriaminepentaacetic acid*

662.0 g (= 700 mmol) of the di - N - methylglucamine salt of the complex salt containing holmium and the diethylenetriaminepentaacetic acid radical listed in Example 5 are made into a paste with 600 ml of water *p.i.* and, after the solution of 1.8 g of tromethamine, dissolved by making up the volume to 1000 ml with water *p.i.* heating slightly. The solution is placed in ampoules and heat-sterilised.

*Example 38*

*Preparation of a solution of the di - N - methylglucamine salt of the ytterbium(III) complex of diethylenetriaminepentaacetic acid*

476.9 g (= 500 ml) of the di - N - methylglucamine salt of the complex salt containing ytterbium and the dethylenetriaminepentaacetic acid radical listed in Example 5 are made into a paste with 650 ml of water *p.i.* and, after the addition of 1.5 g of tromethamine, dissolved by making up the volume to 1000 ml with water *p.i.*. The solution is placed in ampoules and heat-sterilised.

*Example 39*

*Preparation of a solution of the disodium salt of the lanthanum(III) complex of diethylenetriaminepentaacetic acid*

573.2 g (= 1000 mmol) of the disodium salt of the complex salt containing lanthanum and diethylenetriaminepentaacetic acid radical listed in Example 6 are made into a paste in 650 ml of water *p.i.* and dissolved by making up the volume to 1000 ml with water *p.i.*. The solution is placed in ampoules and heat-sterilised.

*Example 40*

*Preparation of a solution of the disodium salt of the dysprosium(III) complex of diethylenetriaminepentaacetic acid*

477.4 g (= 800 mmol) of the disodium salt of the complex salt containing dysprosium and the diethylenetriaminepentaacetic acid radical listed in Example 6 are made into a paste in 600 ml of water *p.i.* and dissolved by making up the volume to 1000 ml with water *p.i.*. The solution is placed in ampoules and heat-sterilised.

*Example 41*

*Preparation of a solution of the disodium salt of the holmium(III) complex of diethylenetriaminepentaacetic acid*

299.6 g (= 500 mmol) of the disodium salt of the complex salt containing holmium and the diethylene triaminepentaacetic acid radical listed in Example 6 are made into a paste in 500 ml of water *p.i.* and dissolved by making up the volume to 1000 ml with water *p.i.*. The solution is placed in ampoules and heat-sterilised.

*Example 42*

*Preparation of a solution of the disodium salt of the ytterbium(III) complex of diethylenetriaminepentaacetic acid*

303.5 g (= 500 mmol) of the complex salt containing ytterbium listed in Example 6 are made into a paste in 500 ml of water *p.i.* and dissolved by making up the volume to 1000 ml with water *p.i.*. The solution is placed in ampoules and heat-sterilised.

*Example 43*

*Preparation of a solution of the tetra- N - methylglucamine salt of the gadolinium(III) complex of ethylenedinitrolo - tetrakis (methanephosphonic acid)*

137.1 g (= 100 mmol) of the complex salt described in Example 12 are made into a paste in 500 ml of water *p.i.* and, after the addition of 0.8 g of tromethamine, dissolved by making up the volume to 1000 ml with water *p.i.*. The solution is placed in ampoules and heat-sterilised.

*Example 44*

*Preparation of a solution of the gadolinium(III) complex of N' - (2 - hydroxyethyl) - ethylenediamine - N,N,N' - triacetic acid*

1.9 g (= 6.7 mmol) of N' - (2 - hydroxyethyl) - ethylenediamine - N,N,N' - triacetic acid and 1.2 g (= 3.35 mol) of gadolinium(III) oxide are dissolved in 6 ml of water *p.i.* while heating. The solution is placed in ampoules and heat-sterilised.

*Example 45*

*Preparation of a solution of the disodium salt of the manganese(II) complex of trans - 1,2 - cyclohexylenediaminetetraacetic acid*

Under nitrogen, 44.3 g (= 100 mmol) of the complex salt described in Example 9 are made into a paste in 60 ml of water *p.i.* and dissolved by making up the volume to 100 ml with water *p.i.*. The solution is placed in ampoules and heat-sterilised.

*Example 46*

*Preparation of a solution of the sodium salt of the gadolinium(III) complex of 1,4,8,11 - tetraazacyclotetradecane - N,N',N'',N''' - tetraacetic acid*

552.6 g (= 1 mol) of the complex salt containing gadolinium and the 1,4,8,11 - tetraazacyclotetradecanetetraacetic acid radical listed in Example 11 are dissolved in water *p.i.* and made up to 1000 ml. The solution is placed in bottles and heat-sterilised.

*Example 47*

*Preparation of a solution of the disodium salt of the*

*bismuth(III) complex of diethylenetriamine-pentaacetic acid*

23.4 g (= 50 mmol) of bismuth(III) oxide are suspended in 50 ml of water *p.i.*. After the addition of 39.3 g (= 100 mmol) of diethylenetriamine-pentaacetic acid and 4.0 g (= 50 mmol) of caustic soda, the whole is refluxed until a clear solution is obtained. The solution, cooled to room temperature, is neutralised by adding 4.0 g of caustic soda and made up to 100 ml with water *p.i.*. The solution is introduced into ampoules and heat-sterilised.

*Example 48*

*Preparation of a solution of the disodium salt of the samarium (III) complex of diethylenetriamine-pentaacetic acid*

58.5 g (= 100 mmol) of the complex salt containing samarium listed in Example 6 are dissolved in 65 ml of water *p.i.* while heating. Water *p.i.* is added to make a total volume of 100 ml, and the solution is introduced into ampoules and heat-sterilised.

*Example 49*

*Preparation of a solution of the di-N-methylglucamine salt of the gadolinium(III) complex of 13,23-dioxo-15,18,21-tris(carboxymethyl)-12,15,18,21,24-pentaazapentatriacontanoic diacid*

130.4 g (= 100 mmol) of the di-N-methylglucamine complex salt listed in Example 2 are made into a paste in 250 ml of water *p.i.* and dissolved while heating. The solution is made up to 500 ml with water *p.i.*, introduced into ampoules and heat-sterilised.

*Example 50*

*Preparation of a solution of the di-N-methylglucamine salt of the manganese(II) complex of ethylenediaminetetraacetic acid*

3.68 g (= 5 mmol) of the complex salt containing manganese and the ethylenediaminetetraacetic acid radical listed in Example 9 are dissolved in 70 ml of water *p.i.*, and 0.4 g of sodium chloride is added to the solution. The solution is then made up to 100 ml with water *p.i.* and introduced into ampoules through a sterile filter. The solution is at 280 mOsm isotonic with blood.

*Example 51*

*Preparation of a solution of the disodium salt of the gadolinium(III) complex of diethylenetrinitrolo-penta-(methane phosphonic acid)*

38.57 g (= 50 mmol) of the disodium salt of the complex containing gadolinium and the diethylenetrinitrolo-penta(methanephosphonic acid) listed in Example 12 are made into a paste with 50 ml of water *p.i.*. The pH is adjusted to 7.2 by adding caustic soda powder and the volume is made up to 100 ml with water *p.i.*. The solution is introduced into ampoules and heat-sterilised.

*Example 52*

*Preparation of a solution of the trisodium salt of the manganese(II) complex of diethylenetriamine-pentaacetic acid*

Under nitrogen, 39.3 g (= 100 mmol) of diethylenetriaminepentaacetic acid are suspended in 100 ml of water *p.i.*, and 11.5 g of manganese(II) carbonate are added. The whole is heated to 95°C and 300 ml of 1N sodium hydroxide solution are added dropwise. The neutral solution is sterile-filtered and introduced into ampoules.

*Example 53*

*Composition of a powder for the preparation of a suspension*

| | | |
|---|---|---|
| 4.000 | g | gadolinium(III) complex of diethylenetriaminepentaacetic acid (water content 8.0%) |
| 3.895 | g | saccharose |
| 0.100 | g | polyoxyethylenepolyoxypropylene polymer |
| 0.005 | g | aromatic substance |
| 8.000 | g | |

*Example 54*

*Preparation of a solution of the gadolinium(III) complex of the conjugate of diethylenetriamine-pentaacetic acid with human serum albumen*

10 mg of 1,5-bis(2,6-dioxomorpholino)-3-azapentane-3-acetic acid are added to 20 ml of a solution of 3 mg of the protein in a 0.5 molar sodium bicarbonate buffer (pH 7-8). The whole is stirred for 30 minutes at room temperature and is then dialysed against a 0.3 molar sodium phosphate buffer. 50 mg of gadolinium(III) acetate are then added and purification is effected by gel chromatrography over a Sephadex G25 column. The fraction obtained is sterile-filtered and placed in multi-dose phials. Freeze-drying produces a dry preparation that can be stored.

In an analogous manner, there is obtained with immunoglobulin a solution of the corresponding complex conjugate.

*Example 55*

*Preparation of a solution of the gadolinium(III) complex of the conjugate of diethylenetriamine-pentaacetic acid (DTPA) with a monoclonal antibody*

1 mg of amixed DTPA anhydride (obtained, for example, from DTPA and isobutyl chloroformate) is added to 20 µl of a solution of 0.3 mg of a monoclonal antibody in a 0.05 molar sodium bicarbonate buffer (pH 7-8) and the whole is stirred for 30 minutes at room temperature. Dialysis is carried out against a 0.3 molar sodium phosphate buffer, and 2 mg of the gadolinium(III) complex of ethylenediaminetetraacetic acid (EDTA) are added to the antibody fraction obtained. After purification by gel chromatography over Sephadex G25, the sterile-filtered solution is placed in multi-dose phials and freeze-dried.

Using the mixed anhydride of *trans*-1,2-diaminocyclohexanetetraacetic acid (CDTA) there is obtained in analogous manner, a solution of the corresponding gadolinium(III) complex of the CDTA antibody.

Using the manganese(II) complex of ethylenediaminetetraacetic acid there is obtained in an analogous manner the manganese(II) complexes of the antibodies coupled with DTPA or CDTA.

*Example 56*

*Preparation of a solution of the gadolinium(III) complex of the conjugate of 1-phenyl-ethylenediaminetetraacetic acid with immunoglobulin*

According to the procedure described in J. Med. Chem. 1974, vol. 17, p. 1307, a 2% solution of the protein in a 0.12 molar sodium bicarbonate solution containing 0.01 mol of ethylenediaminetetraacetic acid is cooled to +4°C and there is added dropwise the proportion, equivalent to the protein, of a freshly prepared ice-cold diazonium salt solution of 1-(*p*-aminophenyl)-ethylenediaminetetraacetic acid. The

whole is stirred overnight (pH 8.1) at +4°C and is then dialysed against a 0.1 molar sodium citrate solution. When dialysis is complete, an excess of gadolinium(III) chloride is added to the solution of the conjugate and ultra-filtration is carried out to remove ions. Finally, the sterile-filtered solution is placed in multi-dose phials and freeze-dried.

*Example 57*

*Preparation of a colloidal dispersion of a Mn(II) - CDTA - lipid conjugate*

0.1 mmol of distearoylphosphatidylethanolamine and 0.1 mmol of the disanhydride of *trans* - 1,2 - diaminocyclohexanetetraacetic acid in 50 ml of water are stirred at room temperature for 24 hours. 0.1 mmol of manganese(II) carbonate is added and stirring is again carried out at room temperature for 6 hours. After purification over a sephadex G50 column, the sterile-filtered solution is placed in multi-dose phials and freeze-dried.

A colloidal dispersion of the gadolinium - DTPA - lipid conjugate can be obtained analogously with gadolinium(III) oxide.

*Example 58*

*Preparation of lipsomes charged with gadolinium(III) - DTPA*

According to the procedure described in Proc. Natl. Acad. Sci. U.S.A. 75, 4194, a lipid mixture comprising 75 mol % of egg phosphatidylchloline and 25 mol % of cholestrol is prepared as a dry substance. 500 mg thereof are dissolved in 30 ml of diethyl ether and, in an ultrasonic bath, 3 ml of a 0.1 molar solution of the di - N - methylglucamine salt of the gadolinum(III) complex of diethylenetriaminepentaacetic acid in water *p.i.* are added dropwise thereto. When the addition of the solution is complete, the exposure to ultrasonic waves is continued for 10 minutes and then concentration is carried out in a rotary evaporator. The gel-like residue is suspended in a 0.125 molar sodium chloride solution and, at 0°C, repeatedly freed of non-encapsulated contrast agent portions by centrifugation (20000 g/29 minutes). Finally, the lipsomes so obtained are freeze-dried in multi-dose phials. The preparation is administered as a colloidal dispersion in a 0.9 % by weight sodium chloride solution.

CLAIMS

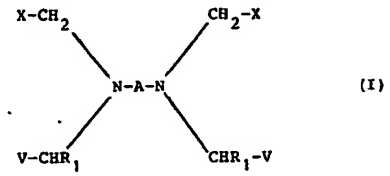
1. A diagnostic preparation which comprises (i) a physiologically tolerable complex salt which contains (a) a central element selected from elements having atomic numbers of from 21 to 29, 42, 44 and from 57 to 83, and (b) a radical of a physiologically-tolerable complex-forming acid and, if desired, (c) a radical selected from radicals of inorganic and organic bases and amino acids, and (ii) a physiologically tolerable carrier.

2. A diagnostic preparation as claimed in claim 1, wherein the carrier is an aqueous carrier.

3. A diagnostic preparation as claimed in claim 2, wherein the carrier is water or physiological salt solution, and the complex salt is dissolved or suspended in it.

4. A diagnostic preparation as claimed in claim 2 or claim 3, wherein the complex salt is present in a concentration of from 1 µmol to 1 mol per litre.

5. A diagnostic preparation as claimed in any one of claims 1 to 4, wherein the physiologically tolerable complex salt is a compound of the general formula



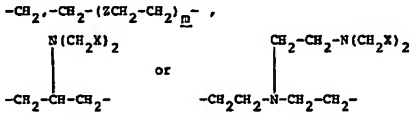
(I)

in which

X represents the radicals $-COOY$, $-PO_3HY$ or $-CONHOY$ wherein Y represents a hydrogen atom, a metal equivalent and/or a physiologically tolerable cation of an inorganic or organic base or amino acid.

and in which

A represents the group $-CHR_2-CHR_3-$,



or



in which

X has the meanings given above,

$R_1$ represents in each case a hydrogen atom or methyl group,

$R_2$ and $R_2$ together represent a trimethylene group or a tetramethylene group,

or each represent a hydrogen atom, lower alkyl radical, phenyl radical or benzyl radical, or

$R_2$ represents a hydrogen atom

and

$R_3$ represents a group $-(CH_2)_p-C_6H_4-W-$protein in which

*p* represents 0 or 1,

W represents $-NN-$ or $NHCOCH_2-$

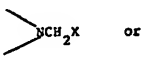
and

-protein represents a protein radical

and

*m* represents the integer 1, 2 or 3,

Z represents an oxygen atom or a sulphur atom or the group



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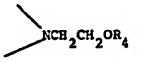


in which

X has the meanings given above

and

$R_4$ represent a lower alkyl radical,

and in which

V has the same meaning as X or represents the group $-CH_2OH$, $-CONH(CH_2)_nX$ or $-COB$

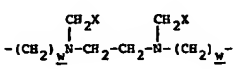
in which

X has the meanings given above,

B represents a protein or lipid radical

and

*n* represents the integers from 1 to 12 or if $R_1$, $R_2$ and $R_3$ are hydrogen atoms both V's together represent the group



in which

X has the meanings given above

and

*w* represents the integer 1, 2 or 3,
with the proviso that at least two of the substituents Y are metal equivalents in which the metal has an atomic number of from 21 to 29, 42, 44 or from 57 to 83.

6. A diagnostic preparation as claimed in any one of claims 1 to 5, wherein the complex-forming acid is diethylenetriaminepentaacetic acid.

7. A diagnostic preparation as claimed in any one of claims 1 to 5, wherein the complex-forming acid is ethylenediaminetetraaccetic acid.

8. A diagnostic preparation as claimed in any one of claims 1 to 5, wherein the complex-forming acid is *trans*-1,2-cyclohexylenediaminetetraacetic acid, 1,4,7,10-tetraazacyclododecanetetraacetic acid or 13,23-dioxo-15,18,21-tris-(carboxymethyl)-12,15,18,21,24-pentaazapentatriacontanoic diacid.

9. A diagnostic preparation as claimed in any one of claims 1 to 8, wherein the complex-forming acid is linked as a conjugate with a biomolecule.

10. A diagnostic preparation as claimed in claim 9, wherein the biomolecule is insulin or a prostaglandin, steroid hormone, amino sugar, peptide, protein or lipid.

11. A diagnostic preparation as claimed in claim 9, wherein the biomolecule is an albumen.

12. A diagnostic preparation as claimed in claim 9, wherein the biomolecule is a monoclonal antibody.

13. A diagnostic preparation as claimed in claim 12, wherein the monoclonal antibody is specific to tumour-associated antigens.

14. A diagnostic preparation as claimed in claim 9, wherein the complex-forming acid forms a conjugate or inclusion compound with a lipsome.

15. A diagnostic preparation as claimed in any one of claims 1 to 4, wherein the complex salt (i) is the di-N-methylglucamine salt of the manganese(II) complex of ethylenediaminetetraacetic acid.

16. A diagnostic preparation as claimed in any one of claims 1 to 4, wherein the complex salt (i) is the di-N-methylglucamine salt of the gadolinium(III) complex of diethylenetriaminepentaacetic acid.

17. A diagnostic preparation as claimed in any one of claims 1 to 4, wherein the complex salt (i) is the di-N-methylglucamine salt of the dysprosium(III) complex of diethylenetriaminepentaacetic acid.

18. A diagnostic preparation as claimed in any one of claims 1 to 4, wherein the complex salt (i) is the monosodium/mono-N-methylglucamine mixed salt of the gadolinium(III) complex of diethylenetriaminepentaacetic acid.

19. A diagnostic preparation as claimed in any one of claims 1 to 4, wherein the complex salt (i) is the dilysine salt of the gadolinium(III) complex of diethylenetriaminepentaacetic acid.

20. A diagnostic preparation as claimed in any one of claims 1 to 4, wherein the complex salt (i) is the disodium salt of the gadolinium(III) complex of diethylenetriaminepentaaccetic acid.

21. A diagnostic preparation as claimed in any one of claims 1 to 4, wherein the complex salt (i) is the iron(III) complex of diethylenetriaminepentaacetic acid.

22. A diagnostic preparation as claimed in any one of claims 1 to 4, wherein the complex salt (i) is the disodium salt of the iron(III) complex of diethylenetriaminepentaacetic acid.

23. A diagnostic preparation as claimed in any one of claims 1 to 4, wherein the complex salt (i) is the disodium salt of the manganese(III) complex of diethylenetriaminepentaacetic acid.

24. A diagnostic preparation as claimed in any one of claims 1 to 4, wherein the complex salt (i) is the di-N-methylglucamine salt of the holmium(III) complex of diethylenetriaminepentaacetic acid.

25. A diagnostic preparation as claimed in any one of claims 1 to 4, wherein the complex salt (i) is the disodium salt of the manganese(II) complex of ethylenediaminetetraacetic acid.

26. A diagnostic preparation as claimed in any one of claims 1 to 4, wherein the complex salt (i) is the di-N-methylglucamine salt of the bismuth(III) complex of diethylenetriaminepentaacetic acid.

27. A diagnostic preparation as claimed in any one of claims 1 to 4, wherein the complex salt (i) is the di-N-methylglucamine salt of the manganese(II) complex of *trans*-1,2-cyclohexylenediaminetetraacetic acid.

28. A diagnostic preparation as claimed in any one of claims 1 to 4, wherein the complex salt (i) is the disodium salt of the ytterbium(III) complex of diethylenetriaminepentaacetic acid.

29. A diagnostic preparation as claimed in any one of claims 1 to 4, wherein the complex salt (i) is the N-methylglucamine salt of the gadolinium(III) complex of 1,4,7,10-tetraazacyclododecanetetraacetic acid.

30. A diagnostic preparation as claimed in any one of claims 1 to 4, wherein the complex salt (i) is the disodium salt of the manganese(II) complex of *trans*-1,2-cyclohexylenediaminetetraacetic acid.

31. A diagnostic preparation as claimed in any one of claims 1 to 4, wherein the complex salt (i) is the disodium salt of the bismuth(III) complex of diethylenetriaminepentaacetic acid.

32. A diagnostic preparation as claimed in any one of claims 1 to 4, wherein the complex salt (i) is the di-N-methylglucamine salt of the gadolinium(III) complex of 13,23-dioxo-15,18,21-tris-(carboxymethyl)-12,15,18,21,24-pentaazapentatriacontanoic diacid.

33. A diagnostic preparation as claimed in any one of claims 1 to 4, wherein the complex salt (i) is the sodium salt of the gadolinium(III) complex of 1,4,7,10-tetraazacyclododecanetetraacetic acid.

34. A diagnostic preparation as claimed in any one of claims 1 to 4, wherein the complex salt (i) is the gadolinium(III) complex of the conjugate of diethylenetriaminepentaacetic acid with immunoglobulin.

35. A diagnostic preparation as claimed in any one of claims 1 to 4, wherein the complex salt (i) is the gadolinium(III) complex of the conjugate of diethylenetriaminepentaacetic acid with human serum albumen.

36. A diagnostic preparation as claimed in any one of claims 1 to 4, wherein the complex salt (i) is the gadolinium(III) complex of the conjugate of diethylenetriaminepentaacetic acid with a monoclonal antibody.

37. A diagnostic preparation as claimed in any one of claims 1 to 4, wherein the complex salt (i) is the manganese (II) complex of the conjugate of *trans* - 1,2 - cyclohexylenediaminetetraacetic acid with a monoclonal antibody.

38. A diagnostic preparation as claimed in any one of claims 1 to 4, wherein the complex salt (i) is the manganese(II) complex of the lipid conjugate of *trans* - 1,2 - cyclohexylenediaminetetraacetic acid.

39. A diagnostic preparation as claimed in any one of claims 1 to 4, wherein the complex salt (i) is the gadolinium(III) complex of diethylenetriamine-pentaacetic acid conjugated with a lipsome.

40. A diagnostic preparation as claimed in any one of claims 1 to 4, wherein the complex salt (i) is the disodium salt of the holmium(III) complex of diethylenetriaminepentaacetic acid.

41. A diagnostic preparation as claimed in any one of claims 1 to 4, wherein the complex salt (i) is the disodium salt of the lanthanum(III) complex of diethylenetriaminepentaacetic acid.

42. A diagnostic preparation as claimed in any one of claims 1 to 4, wherein the complex salt (i) is the di - N - methylglucamine salt of the ytterbium(III) complex of diethylenetriaminepentaacetic acid.

43. A diagnostic preparation as claimed in any one of claims 1 to 4, wherein the complex salt (i) is the disodium salt of the samarium(III) complex of diethylenetriaminepentaacetic acid.

44. A diagnostic preparation as claimed in any one of claims 1 to 4, wherein the complex salt (i) is the disodium salt of the gadolinium(III) complex of 13,23 - dioxo - 15,18,21 - tris - (carboxymethyl) - 12,15,18,21,24 - pentaazapentatriacontanoic diacid.

45. A diagnostic preparation as claimed in any one of claims 1 to 4, wherein the physiologically tolerable complex salt contains a central element selected from elements having an atomic number of from 71 to 83.

46. A diagnostic preparation as claimed in claim 1, substantially as described in any one of Examples 14 to 58 herein.

47. A diagnostic preparation as claimed in any one of claims 1 to 45, which is a dosage form suitable for administration orally, neurally or intravasally.

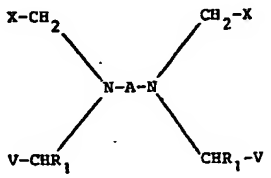
48. An ampoule containing a diagnostic preparation as claimed in any one of claims 1 to 45, in a form suitable for injection.

49. A process for the manufacture of a diagnostic preparation as claimed in any one of claims 1 to 45, wherein the complex salt (i) is dissolved or suspended in water or phsiological salt solution, and is made up, if desired with the incorporation of one or more physiologically tolerable adjuncts, in a form that is suitable for intravasal or oral administration.

50. A physiologically tolerable complex salt which contains (a) a central element selected from elements having atomic numbers of from 21 to 29, 42, 44 and from 57 to 83, and (b) a radical of a physiologically tolerable complex-forming acid and, if desired, (c) a radical selected from radicals of inorganic and organic bases and amino acids.

51. A physiologically tolerable complex salt as claimed in claim 50, wherein the central element (a) is one selected from elements having atomic numbers of from 71 to 83.

52. A physiologically tolerable complex salt of the general formula




(I)

in which X, A, V and $R_1$ have the meanings give in claim 5, with the proviso that it contains from 3 to 12 substituents Y of which at least two are metal equivalents in which the metal has an atomic number of from 21 to 29, 42, 44 or from 57 to 83 and, in addition, at least one of the substituents Y is a physiologically tolerable cation of an organic base or amino acid, any substituents Y which may remain being hydrogen atoms or cations of an inorganic base.

53. Any one of the physiologically tolerable complex salts specified in any one of the Examples herein.

54. The N - methylglucamine salt of the gadolinium(III) complex of ethylenediaminetetraacetic acid.

55. The di - N - methylglucamine salt of the gadolinium(III) complex of diethylenetriamine-pentaacetic acid.

56. The di - N - methylglucamine salt of the iron(III) complex of diethylenetriaminepentaacetic acid.

57. The di - N - methylglucamine salt of the maganese(II) complex of ethylenediaminetetraacetic acid.

58. The disodium salt of the gadolinium(III) complex of diethylenetriaminepentaacetic acid.

59. The tri - N - methylglucamine salt of the manganese(II) complex of diethylenetriamine-pentaacetic acid.

60. The N - methylglucamine salt of the dysprosium(III) complex of ethylenediamine-tetraacetic acid.

61. The di - N - methylglucamine salt of the holmium(III) complex of diethylenetriamine-pentaacetic acid.

62. The dilysine salt of the gadolinium(III) complex of diethylenetriaminepentaacetic acid.

63. The di - N - methylglucamine salt of the manganese(II) complex of *trans* - 1,2 - cyclohexylene-tetraacetic acid.

64. The di - N - methylglucamine salt of the bismuth(III) complex of diethylenetriamine-pentaacetic acid.

65. The disodium salt of the ytterbium(III) complex of diethylenetriaminepentaacetic acid.

66. The N - methylglucaine salt of the gadolinium(III) complex of 1,4,7,10 - tetraaza-cyclododecanetetraacetic acid.

67. The N - methylglucamine - sodium - mixed salt of the gadolinium(III) complex of diethylene-triaminepentaacetic acid.

68. A diagnostic preparation which comprises a physiologically tolerable complex salt of the general formula I given in claim 5, with the exception of

preparations for use in NMR diagnostics containing from 5 to 250 mmol per litre of a neutral N-methylglucamine salt of the manganese(II) complex, nickel(II) complex, gadolinium(III) complex, dysprosium(III) complex or holmium(III) complex of ethylenediaminetetraacetic acid or diethylenetriaminepentaacetic acid, or a neutral lysine salt of the gadolinium(III) complex of diethylenetriaminepentaacetic acid, or a neutral sodium or morpholine salt of the manganese(II) complex of ethylenediaminetetraacetic acid, or a neutral diethanolamine salt of the copper(II) complex or cobalt(II) complex of ethylenediaminetetraacetic acid.

69. A processs for the manufacture of a physiologically tolerable complex salt as claimed in any one of claims 50 to 67, substantially as described herein.

70. A method of diagnosis using NMR, wherein a preparation as claimed in any one of claims 1 to 4 in which the complex salt (i) contains an element having an atomic number of from 21 to 29, 42, 44 and from 58 to 70 is administered to a human or animal body.

71. A method of diagnosis using X-rays, wherein a preparation as claimed in any one of claims 1 to 4 and 45 in which the complex salt (i) contains an element having an atomic number of from 57 to 83 is administered to a human or animal body.

72. A method as claimed in claim 71, wherein the complex salt (i) contains an element having an atomic number of from 71 to 83.

73. A method of diagnosis using ultra-sound, wherein a preparation as claimed in any one of claims 1 to 4 is administered to a human or animal body.

74. A physiologically tolerable complex salt containing (a) a central element selected from elements having atomic numbers of from 21 to 29, 42, 44 and from 57 to 83, and (b) a radical of a physiologically tolerable complex-forming acid and, if desired, (c) a radical selected from radicals of inorganic and organic bases and amino acids, for use in a method of diagnosis of the human or animal body by NMR diagnosis, X-ray diagnosis or ultra-sound diagnosis.

75. A physiologically tolerable complex salt as claimed in claim 74, wherein the control element (a) is one selected from elements having atomic numbers of from 71 to 83.

76. A physiologically tolerable complex salt as claimed in any one of claims 52 to 67, for use in a method of diagnosis of the human or animal body by NMR diagnosis, X-ray diagnosis or ultra-sound diagnosis.

77. A process for the manufacture of a diagnostic preparation as claimed in claim 1, conducted substantially as described in any one of Examples 14 to 58 herein.

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